PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	01 MAY 1996
Applicant's or agent's file reference 06519/002WO1	**REPLY DUE** within **TWO** months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US95/06742	26 MAY 1995	27 MAY 1994

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
UNIVERSITY OF COLORADO

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27 SEPTEMBER 1996.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Deborah Freeze /DF BRUCE CAMPELL
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (January 1994)*

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I. Basis of the opinion

1. This opinion has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

[X] the international application as originally filed.

[X] the description, pages 1-40 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.

[X] the claims, Nos. 1-21 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-2 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

3. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:
NONE

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-11, 13-21	YES
	Claims	12	NO
Inventive Step (IS)	Claims	2-5, 21	YES
	Claims	1, 6-20	NO
Industrial Applicability (IA)	Claims	1-20	YES
	Claims	21	NO

2. CITATIONS AND EXPLANATIONS

Claim 12 lacks novelty under PCT Article 33(2) as being anticipated by Selawry et al. Selawry et al. disclose a method for suppressing rejection of islet cells by also administering Sertoli cells, which express Fas ligand.

Claims 1, 6, 7, 10, 11 and 13-20 lack an inventive step under PCT Article 33(3) as being obvious over Takahashi et al (Cell, 1994). Takahashi et al. disclos the sequence of the mouse Fas ligand (Fig. 1). Takahashi et al. teach that the Fas ligand induces apoptosis in Fas-expressing cells (page 972, column 2). Takahashi et al. teach that activated T cells express Fas, and suggest that Fas ligand is involved in induction of peripheral tolerance (page 973). Takahashi et al. do not teach pharmaceutical compositions or clinical methods.
It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a pharmaceutical composition comprising the mouse Fas ligand. One would have been motivated to do so, given the known effect of Fas ligand in causing apoptosis in mature activated T cells. There would have been a reasonable expectation that so killing activated T cells would have suppressed T cell mediated phenomena, such as graft rejection, T cell mediated disease or disease recurrence, and inflammation. Similarly, it would have been obvious that detection of Fas ligand would be useful in selecting suitable graft donor tissue or graft recipient sites. Thus the invention as a whole was *prima facie* obvious to one of ordinary skill in the art.

Claims 8 and 9 lack an inventive step under PCT Article 33(3) as being obvious over Takahashi et al (Cell, 1994) in view of Johnstone et al and Lee et al. Takahashi et al disclose the mouse Fas ligand, as discussed above. Takahashi et al. do not disclose antibodies against the Fas ligand. Johnstone et al teach methods for producing antibodies. Lee et al teach a method for determining what cell types express Fas, utilizing an antibody against Fas.
It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Johnstone (Continued on Supplemental Sheet.)

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VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 7 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claim is indefinite for the following reason(s): "human Fas ligand" has no antecedent basis. It was assumed that "mouse" was intended, since the human ligand is claimed in claim 3.

It is noted for the record that U.S. application 08/250,478 did not disclose the sequence of the human Fas ligand in sufficient detail to enable one killed in the art to make the invention of claims 2-5. The human sequence was disclosed in U.S. application 08/378,507. However, the Takahashi et al (International Immunology, 1994) reference was published before 08/378,507 was filed.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A01N 37/18, 63/00; A61K 38/00; C07H 21/04; C07K 1/00, 6/00; C12N 15/00 and US Cl.: 424/93.1, 93.2, 93.21; 435/172.3, 320.1; 514/2; 530/350, 387.1; 536/23.5, 23.51

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
et al. to produce antibodies against the Fas ligand disclosed by Takahashi et al. One would have been motivated to do so in order to study expression of the Fas ligand in a manner analogous to that used by Lee et al. Thus the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 21 lacks industrial applicability as defined by PCT Article 33(4). Immune "protection" is provided by the Fas ligand protein, not the DNA encoding it. Therefore, in the event that a gene or a viral vector were attacked by activated host T cells, it is not expected that physical attachment of the DNA sequence would provide any protection.

Claims 1 and 6-20 meet the criteria set out in PCT Article 33(4).

Claims 1, 6-11 and 13-21 meet the criteria set out in PCT Article 33(2).

Claims 2-5 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the sequence of the human Fas ligand.

---------- NEW CITATIONS ----------

SELAWRY et al. Sertoli cell-enriched fractions in successful islet cell transplantation. Cell Transplantation. 1993, Vol. 2, pages 123-129, see the entire document.